

AMENDMENTS TO THE SPECIFICATION

Kindly amend the paragraph starting at page 2, line 1, as follows.

Many molecular derivatives of GLP-1 have been reported. For instance, GLP-1 (7-37) (SEQ ID NO:1) is known. A variety of analogs have also been described eg., Gln⁹-GLP-1 (7-37) (SEQ ID NO:15), D-Gln⁹-GLP-1 (7-37), acetyl-Lys⁹-GLP-1 (7-37) (SEQ ID NO:16), Thr¹⁶-Lys¹⁸-GLP-1(7-37) (SEQ ID NO:17), and Lys¹⁸-GLP-1 (7-37) (SEQ ID NO:18), Gly⁸-GLP-1 (7-37) (SEQ ID NO:19), and Ser⁸-GLP-1 (7-37) (SEQ ID NO:20). Other GLP-1 derivatives (sometimes called “variants”) have also been reported particularly as acid addition salts, carboxylate salts, lower alkyl esters, and amides. See WO 91/11457 and Mojsov, S., *Int. J. Peptide Protein Research*, 40:333-343 (1992), and references cited therein.

Kindly amend the paragraph starting at page 10, line 4, as follows.

By the phrase “GLP-1 related molecule” is meant a derivative, homologue, variant or analog of GLP-1 including pharmaceutically acceptable salts and free acids thereof. Preferably, the GLP-1 related molecule is a GLP agonist. More specific GLP-1 and GLP-1 related molecules are provided below. GLP-1 analogs, derivatives, variants, precursors and homologues are all suitable for the practice of the invention as long as the active fragment that impacts endogenous insulin production is included. By “GLP-1” is meant

GLP-1(7-37) (SEQ ID NO:1). By custom, the amino-terminus of GLP-1(7-37) (SEQ ID NO:1) has been assigned number 7 and the carboxy-terminus, number 37.

Kindly amend the paragraph starting at page 17, line 16, as follows.

More particular examples of GLP-1 and GLP-1 related molecules ~~including~~ include analogs thereof such as those disclosed in the the PCT/DK00/00393 application.

Such molecules include the following specific compounds:

des Ser³⁹-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:25),

des Pro³⁶-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:26),

des Ala³⁵-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:27),

des Gly³⁴-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:28),

des Ser³⁹-(Lys⁴⁰(palmitoyl))exendin-4(1-39)-Lys₇-NH₂ (SEQ ID NO:29),

des Gly³⁴-(Lys⁴⁰(palmitoyl))exendin-4(1-39)-Lys₇-NH₂ (SEQ ID NO:30),

des Ala³⁵-(Lys⁴⁰(palmitoyl))exendin-4(1-39)-Lys₇-NH₂ (SEQ ID NO:31),

des Pro³⁶-(Lys⁴⁰(palmitoyl))exendin-4(1-39)-Lys₇-NH₂ (SEQ ID NO:32),

Lys⁴⁰(palmitoyl)exendin-4(1-39)-Lys₇-NH₂ (SEQ ID NO:33),

des Pro³⁶,Pro³⁷-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:34),

Lys₆-des Pro³⁶, Pro³⁷, Pro³⁸-exendin-4(1-39)-NH₂, (SEQ ID NO:35),

Asn(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸-exendin-4(1-39)-NH₂, (SEQ ID NO:36),

Lys₆-des Pro³⁶, Pro³⁷, Pro³⁸-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:37),

Asn(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:38),
 des Pro³⁶, Pro³⁷, Pro³⁸-exendin-4(1-39)-Lys₆-NH₂ (SEQ ID NO:39),
 Gly⁸-GLP-1(7-36)-Lys₆-NH₂ (SEQ ID NO:6),
 Lys₆-Gly⁸-GLP-1 (7-36)-Lys₆-NH₂ (SEQ ID NO:7),
 Lys₆-Gly⁸-GLP-1 (7-36)-NH₂ (SEQ ID NO:8),
 (Gly⁸,Lys³⁷(palmitoyl)-GLP-1(7-36)(human)-Lys₇-NH₂ (SEQ ID NO:9),
 (Gly⁸,Lys²⁶(palmitoyl)-GLP-1(7-36)(human)-Lys₆-NH₂ (SEQ ID NO:10),
 Gly⁸,Lys³⁴(palmitoyl)-GLP-1(7-36)(human)-Lys₆-NH₂ (SEQ ID NO:11),
 Gly⁸-GLP-1(7-36)-Lys₈-NH₂ (SEQ ID NO:12),
 Gly⁸-GLP-1(7-36)-Lys₁₀-NH₂ (SEQ ID NO:13),
 Gly⁸-GLP-1(7-37)-Lys₆-NH₂ (SEQ ID NO:14); and the free acid or
 pharmaceutically acceptable salt thereof.

Kindly amend the paragraph starting at page 26, line 4, as follows.

Receptor binding studies. These were carried out at MDS Panlabs, Panlabs
 Taiwan Ltd. In short, CHO-K1 cells harboring the human recombinant GLP-1 receptor
 were harvested. The membrane fraction was purified and used for binding assays.
 COMPOUND 1 and GLP-1 were solubilized in 0.4% DMSO. Membranes were
 incubated with different concentrations of test compounds covering 3 decades of
 concentrations in 20 mM Tris-HCl, pH 7.4, 5 mM MgCl₂, 20 mM NaCl, 1mM leupeptin,

1mM PMSF and 2% BSA for 90 min at 37°C in the presence of 0.03 nM 125 I-GLP-1 (7-36) amide (SEQ ID NO:23). Radioactivity was measured in a γ -counter and IC₅₀-values were determined as the concentrations diminishing the specific binding (total binding minus non-specific binding in the presence of 100 nM GLP-1 (7-36) amide (SEQ ID NO:23)) by 50%.

Kindly amend the paragraph starting at page 26, line 15, as follows.

Binding to human GLP-1 receptors. Concentrations resulting in half-maximal inhibition of binding to the human GLP-1 receptor expressed in CHO-K1 cells were 1.4 ± 0.24 nM and 5.5 ± 1.3 nM for COMPOUND 1 and GLP-1 (7-36) amide (SEQ ID NO:23), respectively. Thus COMPOUND 1 was approximately 4 times more potent as an agonist than GLP-1 (7-36) amide (SEQ ID NO:23).

Kindly amend the specification to replace the sequence listing filed on July 8, 2005 with the sequence listing filed herewith.